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REVIEW

# Ternary Solid Dispersions as an Alternative Approach to Enhance Pharmacological Activity

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**Abstract:** Poor solubility and limited bioavailability remain significant challenges in developing oral drugs, affecting the clinical efficacy of many active pharmaceutical ingredients (APIs). Enhancing solubility has become a primary focus in improving API bioavailability. Among the most commonly employed strategies are amorphous solid dispersions (ASDs) and co-amorphous systems, collectively called binary systems. However, these systems often suffer from wettability and physicochemical limitations, which can hinder drug release. Adding a third component to form ternary solid dispersions (TSDs) significantly enhance drug release and bioavailability, ultimately improving therapeutic outcomes. While numerous studies have investigated the application of TSDs in enhancing API pharmacological activity, only limited studies have a comprehensive analysis of this approach. Therefore, this review aims to summarize and elucidate the mechanisms of TSD systems in improving pharmacological activity. The review includes available literature from Scopus, PubMed, and Google Scholar that utilizes the keywords "ternary solid dispersion" and "pharmacological activity", summarizing the importance of TSDs in therapeutic formulations for enhancing pharmacological activity. Various in vitro and in vivo studies consistently demonstrate that TSDs outperform binary systems by significantly enhancing the pharmacological effects of diverse therapeutic agents, including those with antioxidant, anti-inflammatory, anticancer, antibacterial, anticholinesterase, antihyperlipidemic, anti-hypoglycemic, anti-Alzheimer's, antidiabetic, and hepatoprotective properties. This approach holds significant promise as an alternative for the formulation of low-solubility pharmaceuticals.

**Keywords:** hydrophobic drug, amorphization, ternary solid dispersion, dissolution, pharmacological activity

## Introduction

The development of active pharmaceutical ingredients (APIs) plays a crucial role in modern treatment. APIs serve as the primary ingredient in pharmaceutical formulations, providing therapeutic benefits to patients.[1] They demonstrate pharmacological activity and frequently combined with other excipients to create stable dosage forms that are acceptable to patients.[2] Despite advancements in drug formulation and delivery systems, achieving optimal therapeutic outcomes is still a challenge for many APIs due to their limitations in solubility and bioavailability, which eventually hinder their clinical effectiveness.

Oral administration is the most frequently utilized route for drug delivery.[3–7] However, the development of oral formulations presents several challenges, one of which is the poor solubility of the drug candidates, which would significantly impact their oral bioavailability. The Biopharmaceutics Classification System (BCS) categorizes drugs based on their solubility and permeability, with Class II and IV compounds exhibiting limited bioavailability. This limitation hinders drug absorption and complicates the achievement of optimal therapeutic concentrations in the bloodstream.[8] Consequently, numerous promising drug candidates fail to reach the market or require advanced formulation strategies that increase development complexity. According to current literature, approximately 40% of commercially available drugs exhibit low aqueous solubility, and 40–90% of new drug candidates are also reported to demonstrate poor water solubility.[9–12] Therefore, the development of novel strategies to enhance drug solubility is essential for improving the formulation of poorly water-soluble drugs.

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Researchers have developed several formulation strategies to enhance the solubility and dissolution of poorly soluble drugs.[13,14] Amorphization is one such strategy, as it creates irregular molecules with higher free energy, facilitating dissolution and absorption in the body.[15] However, amorphous drugs without excipients are highly susceptible to recrystallization during storage and dispersion.[16] Amorphous solid dispersions (ASDs) and co-amorphous systems, commonly classified as binary systems, stabilize amorphous drugs, improving their dissolution rates and bioavailability.[17–20] Despite their effectiveness, some binary systems exhibit poor wettability and stability, which can hinder drug release and low solubility.[21,22] Recent studies have investigated ternary solid dispersions (TSDs), where the addition of a third component enhances the physicochemical properties.[23]

A TSD system consists of an API dispersed within two different excipients in solid form. Adding a third component to a binary system enhances both solubility and stability by promoting intermolecular interactions between the API and solubilizer, which reduces the risk of recrystallization.[19] TSDs have also shown significant potential in improving pharmacological activity, as the third component enhances drug release and bioavailability.[20,24] This formulation strengthens drug-biological system interactions, leading to better therapeutic outcomes. It is particularly beneficial for poorly soluble drugs[25] that require advanced strategies to improve pharmacological efficacy.[19]

Despite extensive research on TSD systems for enhancing API solubility in oral drug formulations, studies providing in-depth analyses of their impact on pharmacological activity remain limited. This review aims to elucidate the potential and mechanisms of TSDs in enhancing pharmacological activity through a comprehensive analysis of the current literature while highlighting key findings. Additionally, it proposes future research directions to advance therapeutic strategies for poorly soluble drugs.

## Methods

This review is based on available literature from Scopus, PubMed, and Google Scholar, using the keywords "ternary solid dispersion" and "pharmacological activity". The search focused on studies published since 2014 to ensure relevance to recent advancements. Reviews, opinion pieces, and unrelated studies were excluded. The selected literature specifically examines the role and mechanism of ternary solid dispersion systems in enhancing pharmacological activity. Figure 1 illustrates the study selection process.

## Pharmacological Activity

Pharmacological activity refers to the biochemical or physiological effects of a drug or active compound upon interacting with a biological system.[26] These effects influence various pathways, including enzymatic activity, receptor binding,[27] or intracellular processes.[28,29] This parameter is a key for evaluating therapeutic efficacy, encompassing potency, efficacy, and dose-response relationship, all of which have driven pharmaceutical development.[30,31] Disease treatment widely uses various pharmacologically active compounds, including antibiotics, analgesics, anti-neurodegenerative, anticancer, antiviral, antimicrobial, and anti-diabetic agents.[32] For instance, ibuprofen alleviates pain,[33] while amoxicillin targets bacterial infections,[34] highlighting the role of pharmacological activity in therapeutic interventions.

Beyond the development of pharmacologically potent compounds, conventional therapeutic approaches remain essential in disease management. Conventional drug delivery systems primarily include oral,[35] topical,[36] and parenteral routes.[37] Among these, oral administration is the most common due to its non-invasiveness and ease of use. This trend has led to the widespread adoption of tablets and capsules for API delivery.[38] Their simple formulation enhances patient adherence, supporting their extensive use.[39] Despite their widespread use, oral dosage forms face challenges, particularly with poorly soluble pharmaceuticals.[40] Limited solubility can significantly reduce pharmacological efficacy and therapeutic potential.[41] The key factors contributing to this issue are as follows (Figure 2).

### Solubility of APIs

Molecular size significantly influences drug solubility and ultimately pharmacological efficacy.[42–44] Larger molecules often have lower aqueous solubility, limiting absorption and bioavailability. Research on cytochrome P450 inhibition shows that peak activity increases within a molecular size of the drug range of 300–500 Da but declines beyond this threshold due to poor solubility and reduced target interaction.[45]

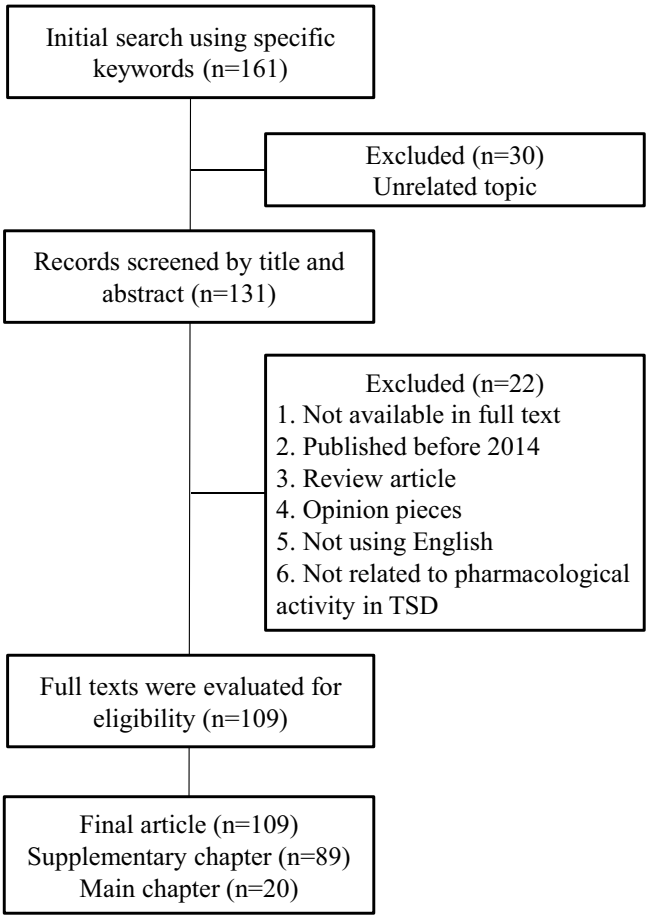


**Figure 1** The study design with the inclusion and exclusion criteria for this review.

## Bioavailability (Pharmacokinetics)

The efficacy of orally administered drugs depends on their dissolution in gastrointestinal fluids and permeability across biological membranes to reach systemic circulation.[46] Poor bioavailability, often due to low absorption or extensive first-pass metabolism, prevents drugs from reaching therapeutic plasma levels. Many drugs act by targeting specific receptors or enzymes, such as statins inhibiting HMG-CoA reductase to lower cholesterol[47] or proton pump inhibitors like omeprazole suppressing gastric acid production.[48] These mechanisms highlight the importance of bioavailability and solubility in optimizing API efficacy.

## Interaction with Biological Targets (Pharmacodynamics)

Many APIs exert their therapeutic effects by selectively targeting receptors, enzymes, or biological pathways. Drug efficacy depends on binding affinity, as low affinity can lead to minimal pharmacological activity.[49] Poor target specificity may also trigger off-target interactions, increasing adverse effects and reducing therapeutic efficacy.[50,51]

## Formulation Considerations

Pharmaceutical stability is essential for maintaining drug efficacy during storage. Instability can cause API degradation, reducing therapeutic effectiveness. Formulation methods also impact stability. For example, amorphous drugs are inherently more unstable due to higher energy levels, leading to recrystallization over time.[16] Therefore, additional techniques are often required to enhance long-term stability and optimize drug performance.

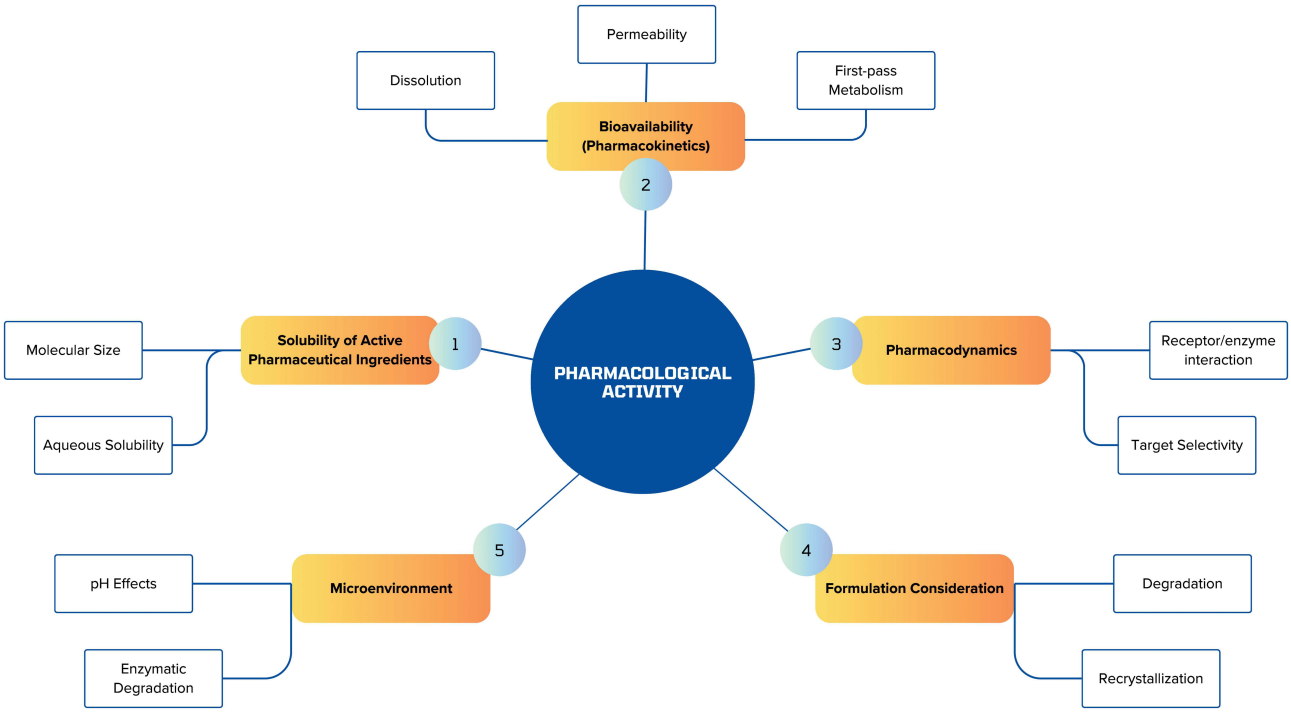


**Figure 2** Key factors influencing pharmacological activity.

## Microenvironment at the Site of Action

The pH of the microenvironment at the target site influences drug solubility, ionization, and efficacy. Suboptimal pH can hinder absorption and reduce therapeutic effects. Additionally, enzymatic activity may degrade the drug prematurely, further limiting its bioavailability and efficacy.[52]

TSD systems offer an innovative solution to overcome these challenges. By utilizing synergistic interactions among multiple components, TSD enhances the solubility, stability, and bioavailability of poorly soluble APIs,[53] ultimately optimizing therapeutic efficacy.

# Ternary Solid Dispersions (TSD)

Binary solid dispersions (BSDs) enhance API solubility and stability by combining polymeric carriers to form amorphous systems. However, they often suffer from limited physical stability, processing constraints, and precipitation during dissolution.[54] To overcome these limitations, TSD contains a third component, such as a secondary polymer, surfactant, small molecule, pH modulator, or adsorbent, to further optimize performance.[55] Studies have demonstrated that TSDs enhance solubility, prevent precipitation, improve stability and processability,[20] which makes them superior to BSDs.[56] The following sections provide detailed discussions of the types of TSD systems, as illustrated in Figure 3.

## API + Polymer + Polymer

This type of TSD employs two polymers, leveraging their distinct physicochemical properties to inhibit crystalline growth,[15] enhance stability,[57] improve wettability, and enable controlled drug release.[58] Al-Obaidi et al found that adding poly[2-hydroxypropyl methacrylate] (PHPMA) to a griseofulvin-polyvinylpyrrolidone (PVP) system enhanced dissolution and wettability through hydrogen bonding.[58] Similarly, Prasad et al demonstrated that the ternary combination of indomethacin with an ionic copolymer of methacrylic acid and methyl methacrylate (Eudragit® 100) and PVP K90 improved stability and dissolution significantly compared to the BSD systems, due to synergistic polymer effects that enhanced drug-polymer interactions and inhibited precipitation from supersaturated solutions.[15]

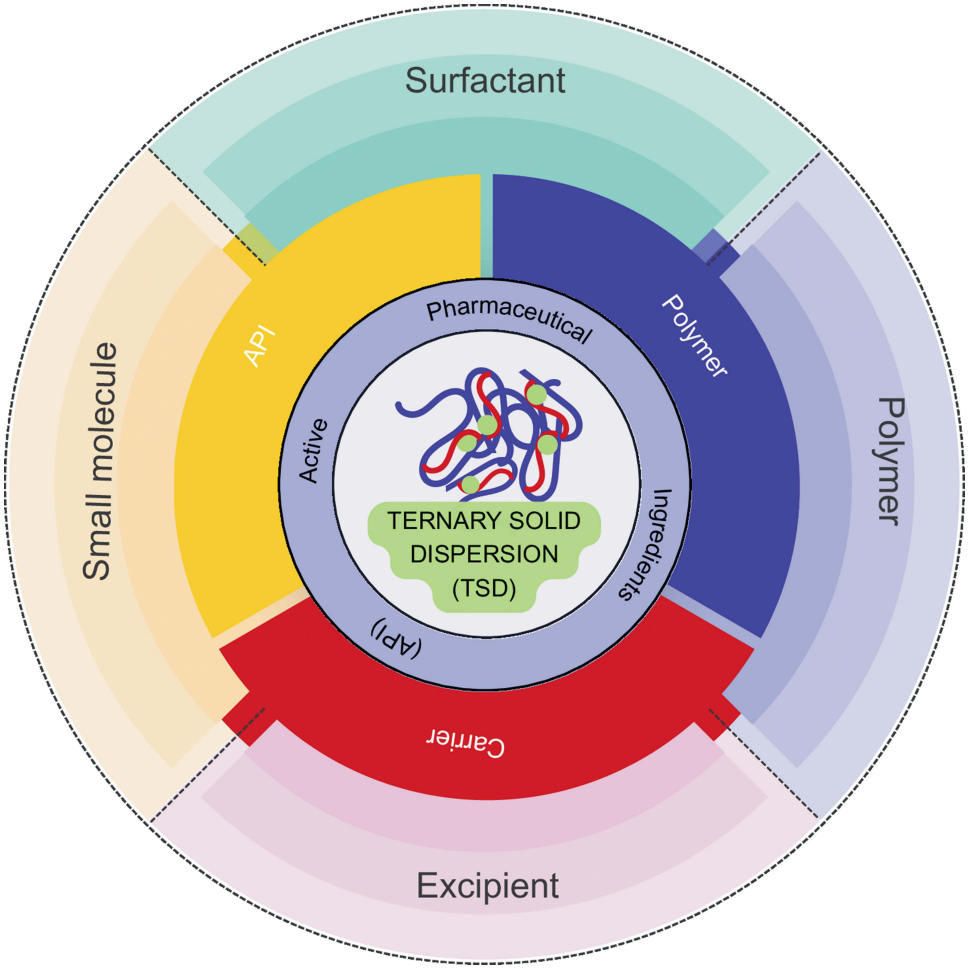


**Figure 3** The type of ternary solid dispersion system. Adapted from Budiman A, Lailasari E, Nurani NV et al. Ternary solid dispersions: A review of the preparation, characterization, mechanism of drug release, and physical stability. *Pharmaceutics*. 2023;15(8):1–30. Creative Commons.[25]

## API + Polymer + Surfactant

Certain TSD formulations disperse a poorly water-soluble drug within a polymer matrix alongside an anionic, cationic, or non-ionic surfactant. These surfactants enhance drug-polymer interactions, improve dispersion, and promote absorption.[59] In some cases, the surfactant molecules synergize with the polymer, forming a coating on the drug particles and subsequently increasing dissolution efficiency.[60] Alhayali et al reported that the addition of Poloxamer 188 into an ezetimibe-PVP K30 system enhances the complex solubility and maintains supersaturation, which is important in improving oral drug absorption and bioavailability.[61] Similarly, Chamsai et al found that D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) reduces interfacial tension and contributes to a more porous structure, improving the solubility of manidipine-copovidone.[62]

## API + API + Polymer

In this approach, researchers integrate multiple APIs into a single system, which is particularly beneficial for combination therapies involving poorly soluble APIs.[20] For instance, the cyclodextrin (CD) complex with darunavir and ritonavir enhances the solubility and stability of ritonavir, which is important because it improves oral bioavailability and enhances pharmacokinetic performance.[63] Similarly, Riekes et al utilized polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) as the carrier for ezetimibe (EZE)/lovastatin (LOV) to improve the dissolution profile of the combination drugs. Their study demonstrated high stability and rapid dissolution, with 92% of EZE and 83% of LOV dissolved within five minutes, which can be attributed to the hydrogen bonding interaction between the APIs and the polymer.[64]

## API + API + Small Molecule

In the context of TSD, the third component can sometimes refer to a small molecule that enhances the initial dissolution rate and stability of the system. Small molecules are non-peptide, biologically active compounds with molecular weights generally below 1000 Da, engineered for high selectivity, potency, and cellular permeability, establishing them as a fundamental component of modern pharmacotherapy due to their stability, ease of administration, and capacity to target diverse diseases.[65,66] It is important to distinguish that when the TSD consists of two APIs, the system may resemble co-amorphous dispersions, where both APIs and the small molecule interact to stabilize the amorphous form and improve drug performance. For example, Wairkar et al utilized magnesium aluminometasilicate (Neusilin®) as a small molecule in the binary combination of nateglinide and metformin hydrochloride (NT-MT). The hydrogen bonding formed between NT, MT, and magnesium aluminometasilicate contributes to stabilizing the amorphous state in this TSD, leading to a notable improvement in NT dissolution, as well as enhancing flow properties and compressibility of the tablet formulation.[67] Similarly, Beyer et al integrated naproxen sodium, a small molecule salt form, into the naproxen-indomethacin binary system using quench-cooling. Their findings demonstrated that the TSD exhibited superior physical stability, with no signs of recrystallization over the 270-day observation period.[68]

## API + Carrier + Excipient

In this context, the carrier refers to a specific type of excipient that functions as the primary medium for dispersing the API, often replacing conventional hydrophilic polymers. Unlike general excipients, which may serve various supporting roles, carriers specifically facilitate homogeneous distribution of the API within the formulation, enhancing solubility and stability. Carriers in this TSD subtype may consist of lipids, pH modulators, and adsorbents (eg a mixture of polyethylene glycol glycerides (Gelucire®50/13), magnesium aluminometasilicate).[20] The solubility of many drugs, typically weak acids or bases, is highly pH-dependent.[69] Hence, the variations in microenvironmental pH would influence drug activity, with weakly acidic drugs showing increased solubility at neutral or alkaline pH levels, while weakly basic drugs show higher solubility at acidic pH.[70] BSDs are often insufficient for solubilizing all pH-dependent drugs,[69] and studies have indicated that TSDs could enhance drug solubility through the addition of pH modulators such as acidifiers and alkalizers and suitable carriers.[71–74] Among the available alkalizers, the addition of 1% NaOH to a binary telmisartan system has been shown to substantially improve solubility by maintaining a stable pH across the dispersion matrix.[75] Citric acid inhibits the recrystallization of the binary GT0918-PVP K30 system and enhances its dissolution through the formation of hydrogen bonding between GT0918 and the citric acid.[76]

BSD formulations often produce waxy products with poor flowability, low compressibility, and difficulty in pulverization.[77,78] Adsorption carriers help address these issues by enhancing surface area, preventing crystal growth, and stabilizing the APIs.[79,80] For instance, porous silica (Sylysia® 350) improved the flowability and compressibility of Bosentan-Poloxamer 188 dispersion, converting them into a free-flowing powder and accelerating drug desorption.[79] Similarly, magnesium aluminometasilicate enhanced the surface area and flowability of carbamazepine-copovidone (Kollidone® VA64) dispersions, leading to an improved dissolution profile.[81]

# Pharmacological Activity of Ternary Solid Dispersions

Previous research has demonstrated the impact of TSD systems on the pharmacological activity of an API, including naturally derived compounds, as summarized in Table 1.

# In vitro Studies of Ternary Solid Dispersion

## Anticancer

Anticancer agents inhibit proliferation, induce apoptosis, or alter signaling in cancer cells.[101] Their efficacy is often screened via in vitro assays like the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay, which quantifies mitochondrial activity as an indicator for cell viability.[98,99] Nonetheless, poor solubility and bioavailability limit the effectiveness of many hydrophobic anticancer agents, necessitating advanced formulations to enhance treatment outcome.

**Table 1** Impact of Ternary Solid Dispersion on Pharmacological Activity

| No. | Active Substance | Polymer | Method | Interaction Mechanisms | Pharmacological Activity | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | In vitro | In vivo | |
| 1. | Simvastatin (SIM) | Polyoxyl 40 Stearate (Myrj 52®) and Polyethylene Glycol (PEG) 12000 | Solvent evaporation | The free O-H region of SIM displayed a minor shift toward reduced wavenumbers, presumably attributable to hydrogen bonding between the hydroxyl (-OH) group of SIM and the functional groups of the carriers, including the carbonyl (C=O) or ether (C-O) groups seen in PEG and polyoxyl 40 stearate. | - | The SIM ternary solid dispersion (TSD) significantly reduced total cholesterol (TC) and triglycerides (TG) in hyperlipidemia induced by a high-fat diet (HFD) over two weeks. The increase in TG levels was 65.52%, 43.38%, 55.16%, and 4.70% in the HFD, SIM, physical mixture, and SIM-TSD groups, respectively, highlighting the superior efficacy of the TSD formulation. | [82] |
| 2. | Glibenclamide (GLB) | Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and Poloxamer 407 | Hot Melt Extrusion (HME) | Hydrogen bonding interactions in the TSD system occur between the GLB, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, and Poloxamer 407. GLB forms hydrogen bonds through its sulfonyl (-$SO_2NH$-), amide (-$CONH_2$), and amine (-NH-) functional groups. In a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, the carbonyl (C=O) and amide (C=O-NH) groups interact with the amide and sulfonyl groups of GLB. Similarly, in Poloxamer 407, the ether (C-O-C) and hydroxyl (-OH) groups establish hydrogen bonds with the amide and amine groups of GLB. | - | Anti-hyperglycemic studies showed a three-fold increase in GLB-TSD oral bioavailability. Rats given a pure GLB suspension maintained blood glucose levels of 120 ± 25 mg/dL at 2–3 hours before rising. The marketed product exhibited a similar trend (110 ± 25 mg/dL at 2 hours). In contrast, GLB-TSD administration resulted in a blood glucose level of 128 ± 17 mg/dL within 0.5 hours, indicating a faster onset of action. | [83] |
| 3. | Curcumin (CUR) | Hydroxypropyl methylcellulose (HPMC) E5 and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer | Solvent evaporation | No new functional groups were detected in the FTIR spectra, indicating the absence of chemical reactions between CUR-HPMC-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. However, variations in peak intensity, particularly in the O-H (3589 $cm^{-1}$) and C=O (1608 $cm^{-1}$) regions, suggest the formation of hydrogen bonds and other physical interactions between CUR, HPMC, and the polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. | CUR, HPMC E5, and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (CUR-TSD) demonstrated a significant improvement in antibacterial activity against both gram-positive (*Staphylococcus aureus, Bacillus cereus*) and gram-negative (*Pseudomonas aeruginosa, Escherichia coli*) pathogens. CUR-TSD also exhibited significantly higher antioxidant activity (93% ± 5.30) compared to CUR (69% ± 4.79). Furthermore, anti-inflammatory testing showed that CUR-TSD effectively protected bovine serum albumin (BSA) from denaturation, with a BSA inhibition rate of 80% ± 3.16 compared to CUR (49% ± 2.91). | - | [84] |
| 4. | Fisetin (FIS) | An ionic copolymer composed of methacrylic acid and methyl methacrylate, and HP-β-cyclodextrin (HPβCD) | Mechanochemical method without solvent | Hydrophobic interactions, hydrogen bonding, and π-stacking interactions enhance the stability and solubility of FIS-TSD. The hydroxyl (-OH) groups of FIS form hydrogen bonds with the carbonyl (C=O) ester groups of an ionic copolymer of methacrylic acid and methyl methacrylate, while their lipophilic regions interact with the hydrophobic cavity of HPβCD. Additionally, π–π stacking occurs between FIS and $IC_{50}$ aromatic residues. | Fisetin- an ionic copolymer of methacrylic acid and methyl methacrylate - HPβCD (FIS-TSD) significantly improved apparent solubility (126.5 ± 0.1 μg·mL−1) compared to the binary system of FIS (FIS-BSD), which showed no detectable solubility. FIS-TSD also exhibited enhanced antioxidant properties (ABTS: $IC_{50}$ = 10.25 μg·mL−1, DPPH: $IC_{50}$ = 27.69 μg/mL, CUPRAC: $IC_{50}$ = 9.52 μg mL−1, FRAP: = 8.56 μg mL−1), whereas FIS-BSD showed no detectable activity. Furthermore, FIS-TSD demonstrated superior neuroprotective effects (AChE inhibition: 39.91%; BChE inhibition: 42.62%) compared to FIS-BSD (AChE inhibition: ~20% and BChE inhibition: ~30%) and pure FIS (AChE inhibition: 0.40% ± 0.03% and BChE inhibition 3.64% ± 0.23%). | - | [85] |

(*Continued*)

**Table 1** (Continued).

| No. | Active Substance | Polymer | Method | Interaction Mechanisms | Pharmacological Activity | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | In vitro | In vivo | |
| 5. | LW6 (3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid methyl ester) | Poloxamer 407 and Povidone (PVP) K30 | Solvent evaporation | The broad shift of the -OH stretching peak and the disappearance of the -NH vibration peak indicate that the LW6 interacts with Poloxamer 407 and PVP K30 through hydrogen bond formation. Additionally, the absence of the carbonyl (C=O) peak at 1698 $CM^{-1}$ suggests hydrogen bonding between LW6 and the proton-donating hydroxyl (-OH) groups of Poloxamer 407 and PVP K30. | - | LW6-Poloxamer 407-PVP K30 (LW6-TSD) enhanced the efficacy of LW6 as a breast cancer resistance protein (BCRP) inhibitor. Co-administration of pure LW6 or LW6-TSD increased topotecan oral exposure by approximately three-fold ($C_{max}$: 91.5 ± 17.7 ng/mL, $T_{max}$: 0.4 ± 0.1 h, AUC: 598 ± 188 ng*h/mL) and ten-fold ($C_{max}$: 326 ± 25.2 ng/mL, $T_{max}$: 1.0 h, AUC: 2140 ± 46.6 ng*h/mL), respectively. | [86] |
| 6. | Silymarin (SL) | PVP and polysorbate 80 (Tween® 80) | Spray drying | The interactions in SL-TSD involve physical adhesion and hydrophilic interactions between SL, PVP, and polysorbate 80. Hydrogen bonding occurs between the hydroxyl (-OH) groups of SL and the carbonyl (C=O) groups of PVP, while the polyoxyethylene chains of polysorbate 80 further enhance solubility by stabilizing SL in the aqueous phase. | - | SL-PVP-polysorbate 80 (SL-TSD) exhibited superior hepatoprotective activity against $CCl_4$-induced liver damage compared to SL and the commercial product. This was evidenced by a significant reduction in serum aspartate transaminase (AST) levels (~1000 U/L) following SL-TSD treatment, whereas no protective effects were observed with SL (~1500 U/L) or the commercial product (~1800 U/L) at the same dose (50 mg/kg/day). Histopathological analysis further confirmed this enhanced hepatoprotective effect, as SL-TSD-treated liver sections displayed reduced hepatocellular necrosis and minimal inflammatory cell infiltration compared to untreated $CCl_4$-exposed livers. | [87] |
| 7. | Silymarin (SM) | Polyvinylpyrrolidone (PVP) and Poloxamer 188 (PL) | Solvent evaporation, microwave irradiation (MI), and freeze-drying (FD) | SM, PVP, and PL form a stable TSD by van der Waals interactions and hydrogen bonding. Hydrogen bonding occurs between the hydroxyl (-OH) groups of SM and the carbonyl (C=O) groups of PVP, while van der Waals interactions arise between the hydrophobic regions of SM and the amphiphilic domains of PL. | The anticancer activity of free SM was evaluated against a lung cancer cell line and compared to SL-PVP-PL (SM-TSD). After 24 hours, SM-TSD exhibited significantly greater cytotoxicity ($IC_{50}$: 171.45 ± 5.2 μg/mL) than free SM did after 48 hours ($IC_{50}$: 321.4 ± 9.4 μg/mL). | - | [88] |
| 8. | Andrographolide (AD) | Polyvinylpyrrolidone/ Kollidon®-SR (PVP) and Poloxamer-407 (P-407) | Solvent evaporation | The hydroxyl (-OH) stretching peak of AD shifted from 3400.12 $cm^{-1}$ to 3415.42 $cm^{-1}$, 3413.95 $cm^{-1}$, and 3414.36 $cm^{-1}$, indicating hydrogen bond formation. Additionally, the carbonyl (C=O) groups of PVP at 1742.69 $cm^{-1}$ and 1639.17 $cm^{-1}$, along with the hydroxyl (-OH) groups of P-407 at 1344.07 $cm^{-1}$, are involved in hydrogen bonding interactions with AD. | - | AD-PVP-P-407 (AD-TSD) demonstrated superior efficacy over pure AD in arthritic Wistar rats. AD-TSD reduced paw edema by 45.79% compared to 29.23% with pure AD and lowered arthritic severity scores. Hepatic markers, AST (86.31 ± 5.69 U/L) and ALT (74.66 ± 3.38 U/L), were significantly lower than in the pure AD group (AST: 118.34 ± 5.17 U/L, ALT: 102.47 ± 4.86 U/L). AD-TSD also reduced TNF-α (97.86 ± 7.83 pg/mL), IL-1β (79.48 ± 4.36 pg/mL), and IL-6 (64.55 ± 4.48 pg/mL) more effectively than pure AD (TNF-α: 125.71 ± 6.82 pg/mL, IL-1β: 107.58 ± 5.91 pg/mL, IL-6: 98.36 ± 5.42 pg/mL). Radiological and histopathological analyses confirmed better joint preservation and reduced inflammation in the AD-TSD group. | [89] |

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|---|---|---|---|---|---|---|---|
| 9. | Andrographolide (AP) | Oxymatrine (OMT) and p-hydroxycinnamic acid (pHCA) | Rotary vacuum evaporation | The hydrogen bonding interactions in the AP-TSD system involve the hydroxyl (-OH) group of AP, which forms hydrogen bonds with the carboxyl (-COOH) groups of pHCA. This interaction is confirmed by the FTIR spectra, where the -OH stretching peak of AP shifted from 3399 $cm^{-1}$ to 3381 $cm^{-1}$, and the carbonyl (C=O) peak shifted from 1727 $cm^{-1}$ to 1754 $cm^{-1}$, indicating strong intermolecular hydrogen bonding between AP and pHCA. | - | The toxicity and anti-Alzheimer's disease activity of AP, AP-OMT (AP-BSD), and AP-OMT-pHCA (AP-TSD) were evaluated using *Caenorhabditis elegans* as an in vivo model. *C. elegans* exposed to AP-TSD at concentrations up to 1.2 mM showed survival rates that were not significantly different from the control group, confirming its safety. In terms of anti-Alzheimer's activity, the mean paralysis time of *C. elegans* treated with 0.6 mM AP-TSD was significantly prolonged compared to AP and AP-BSD, demonstrating its superior efficacy in delaying Aβ-induced paralysis. | [90] |
| 10. | Berberine (BR) | Sodium caprate and PEG 6000 | Solvent evaporation | The FTIR spectra exhibit no additional absorption bands, significant peak shifts, or alterations, indicating the absence of chemical interactions between berberine, sodium caprate, and PEG 6000. The retention of their characteristic peaks suggests that their molecular structures remain unaltered. However, physical interactions, such as molecular distribution, remain a factor influencing the system's properties. | - | BR-sodium caprate-PEG 6000 (BR-TSD) lowered fasting blood glucose to 4.97 ± 0.13 mmol/L, compared to 7.84 ± 0.52 mmol/L for pure BR and 7.96 ± 0.53 mmol/L for the commercial product. Additionally, BR-TSD reduced TG levels to 0.91 ± 0.07 mmol/L and TC to 2.32 ± 0.19 mmol/L, outperforming BR (TG: 1.76 ± 0.18 mol/L, TC: 2.93 ± 0.19 mmol/L) and commercial product (TG: 1.81 ± 0.15 mmol/L, TC: 3.01 ± 0.24 mmol/L). | [91] |
| 11. | Diosmin (DIOS) | β-cyclodextrin (β-CD) and PEG 6000 | Kneading method | The FTIR spectra of the drug compounds showed peak overlap with β-CD in the 400–1300 $cm^{-1}$ range. The bending and stretching vibrations of DIOS were likely constrained by the β-CD cavity, resulting in shifts and broadening of the absorption bands, indicating hydrogen bond interactions. | DIOS-β-CD-PEG 6000 (DIOS-TSD) did not exhibit higher antioxidant activity compared to ascorbic acid (65–98%). However, DIOS-TSD demonstrated the highest antioxidant activity (60–75%) among all tested DIOS formulations, outperforming the DIOS-PEG 6000 (58–65%) and pure DIOS (25–55%) across all concentrations. | - | [92] |
| 12. | Atorvastatin (AT) | PEG 10000 and Poloxamer 188 (P188) | Melting method | AT-PEG 10000-P188 (AT-TSD) demonstrated no chemical interaction, as evidenced by the absence of significant shifts or additional peaks in the FTIR spectra. However, AT-TSD demonstrated physical interactions, such as the homogeneous dispersion of components in the matrix. The retention of ATR's characteristic peaks (3668.1 $cm^{-1}$, 3365 $cm^{-1}$, 1650.7 $cm^{-1}$, and 1579.3 $cm^{-1}$), along with those of PEG 10000 (2888.4 $cm^{-1}$, 1100.2 $cm^{-1}$) and P188 (2889.6 $cm^{-1}$, 1112.2 $cm^{-1}$), in the AT-TSD confirms the absence of chemical modifications while suggesting effective molecular dispersion. | - | On day 7, the AT-TSD demonstrated superior antihyperlipidemic activity, reducing TG (160–190 mg/dL) and TC (115–130 mg/dL) more effectively than AT-PEG (AT-BSD) (TG: 190–220 mg/dL, TC: 130–140 mg/dL) and pure ATR (TG: ~250 mg/dL, TC: ~150 mg/dL). This highlights the enhanced lipid-lowering efficiency of AT-TSD, likely due to improved dissolution and absorption. | [93] |
| 13. | Atorvastatin (ATR) | Croscarmellose sodium/Ac-Di-Sol® SD-711 (CCS) and polyoxyl 40 hydrogenated castor oil/Kolliphor® RH40 (K) | Spray-drying | Adding polyoxyl 40 hydrogenated castor oil RH40 to ATR-CCS enhances intermolecular hydrogen bonding between the drug and polymer chains. FTIR analysis of ATR:CCS: K (ATR-TSD) showed significant increases in vibrational bands associated with aliphatic chains, amidogen, hydroxyl, and carbonyl groups, indicating stronger hydrogen bonding interactions. The presence of Kolliphor® RH40 caused a shift in C=O stretching vibrations (1667.71 $cm^{-1}$ to 1655.07 $cm^{-1}$) and an increase in the intensity of absorption bands at 2920.31, 1655.13, and 1060.95 $cm^{-1}$, further confirming its role in promoting hydrogen bond formation. | - | Efficacy experiments in hyperlipidemic rats demonstrated that ATR-TSD (10 mg/kg) significantly improved lipid profiles and liver function compared to AT-RM. ATR-TSD reduced TC (161.00 ± 12.39 mg/dL), LDL (106.55 ± 13.21 mg/dL), and TG (88.00 ± 16.69 mg/dL), whereas AT-RM resulted in higher LDL (189.87 ± 19.23 mg/dL) and TG (127.40 ± 15.18 mg/dL). Additionally, ATR-TSD lowered AST (120.33 ± 9.50 mg/dL) and ALT (60.00 ± 7.07 mg/dL) more effectively than AT-RM (AST: 154.50 ± 17.62 mg/dL, ALT: 87.75 ± 5.68 mg/dL). | [94] |

(*Continued*)

https://doi.org/10.2147/DDDT.S533359



**Table 1** (Continued).

| No. | Active Substance | Polymer | Method | Interaction Mechanisms | Pharmacological Activity | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | In vitro | In vivo | |
| 14. | Gliclazide (Glc) | HPβCD and Tryptophan (Tryp) | Solvent evaporation | Tryp interacts with Glc through hydrogen bonding, π-π stacking, and ionic interactions, preventing its crystallization. The disappearance of the $NH_3^+$ asymmetric angular deformation band at 1658 $cm^{-1}$ and the emergence of a new intense band at 1632 $cm^{-1}$ indicate hydrogen bonding between Tryp and the –OH groups of HPβCD. Additionally, the decreased intensity of the amide bond of Tryp at 1582 $cm^{-1}$ and the –CH mode of the indole ring at 1453 $cm^{-1}$ further confirm the formation of TSD, effectively stabilizing Glc in an amorphous state. | - | Glc-HPβCD-Tryp (Glc-TSD) exhibited superior antioxidant and antidiabetic activity compared to the Glc- HPβCD (Glc-BSD) and Glc alone. The total antioxidant status (TAS) of Glc-TSD was 2.8 ± 0.05 mmol/L, significantly higher than Glc-BSD (2.55 ± 0.04 mmol/L, $p < 0.05$) and Glc alone (2.5 ± 0.06 mmol/L). Similarly, superoxide dismutase (SOD) and catalase (CAT) activities were enhanced in Glc-TSD, reaching 2.72 ± 0.16 U/mg and 2.8 ± 0.05 U/mg, respectively, compared to Glc-BSD (2.55 ± 0.04 U/mg and 2.72 ± 0.16 U/mg) and Glc alone (2.5 ± 0.06 U/mg and 2.5 ± 0.06 U/mg). The antidiabetic evaluation further demonstrated the efficacy of Glc-TSD, reducing blood glucose levels by 49–52%, which was significantly higher than Glc-BSD (45–46%, $p < 0.05$) and Glc alone (38–40%). | [95] |
| 15. | Toltrazuril (TOL) | PEG6000 and $Ca(OH)_2$ | Solvent-fusion method | The reduction in the frequency of the carbonyl band (C=O) at 1695 $cm^{-1}$ and the complete disappearance of the N–H stretching band at 3302.01 $cm^{-1}$ indicate strong hydrogen bonding in the TOL-PEG 6000-$Ca(OH)_2$ (TOL-TSD). This system exhibited the most significant decrease in the C=O peak intensity, suggesting a strong interaction between TOL and $Ca(OH)_2$. These spectral changes confirm the complete amorphization of TOL, contributing to its enhanced water solubility. | The cytotoxic effect of TOL-TSD was higher than that of pure TOL or TOL-PEG 6000 (TOL-BSD). The inhibition rate of *Toxoplasma gondii* increased with drug concentration, reaching approximately 75% at 50 μg/mL and 85% at 100 μg/mL for TOL-TSD, compared to 60% and 70% for TOL-BSD, and 50% and 65% for pure TOL, respectively. | The study evaluated survival rates of Kunming mice infected with the type I RH strain over 21 days. TOL-TSD exhibits the most effective therapeutic response, with all treated mice surviving without signs of alopecia, skin lesions, or organ dysfunction, suggesting its non-toxicity. In contrast, all untreated infected mice died by day 11, while those treated with sulfadiazine succumbed between days 9 and 14. Mice in the TOL and TOL-BSD groups experienced delayed mortality but did not achieve full survival. Additionally, TOL-TSD-treated mice initially lost weight but gradually regained it, which further confirms the treatment's effectiveness. | [96] |
| 16. | Lornoxicam (LOR) | Mixture of polyethylene glycol (GL) and polysorbate 80 | Conventional solvent method | No new chemical interactions were observed between LOR, GL, and polysorbate 80. However, the absence of LOR's crystalline peaks in the TSD suggests that GL contributed to drug amorphization, while polysorbate 80 was likely dispersed within the amorphous matrix without affecting crystallinity | - | LOR-GL-polysorbate 80 (LOR-TSD) exhibits significant anti-inflammatory activity (50%±0.45) compared to LOR-GL (LOR-BSD) (60%±0.7) or pure LOR (70%±1.11). | [97] |
| 17. | Piroxicam (PRX) | Poloxamer 407 (P407) and colloidal silicon dioxide (Aerosil®200) | Melting method | The primary peaks of PRX, its physical mixture, and PRX-P407- colloidal silica dioxide (PRX-TSD) remained unchanged, indicating no significant chemical interaction. The NH and OH stretching vibrations (3335.8 $cm^{-1}$), C=O (1628.1 $cm^{-1}$), and S=O (1341.9 $cm^{-1}$) peaks exhibited minimal shifts, suggesting the absence of strong hydrogen bonding or covalent modifications. | PRX-TSD, commercial piroxicam (Feldene®), and PRX were tested in LPS-induced RAW 264.7 cells at concentrations ranging from 0.1 to 25 μg/mL. At 25 μg/mL, PRX-TSD exhibited the highest nitric oxide (NO) inhibition (30.3 ± 0.1%), outperforming commercial piroxicam (26.6 ± 1.1%) and PRX (7.9 ± 2.5%) ($p < 0.05$). None of the samples showed cytotoxicity. These findings suggest that PRX-TSD enhances both drug release and therapeutic efficacy. | - | [19] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 18. | Chrysin (CRI) | Lauryl ether (Brij®L4) and aminoclay | Solvent evaporation | No significant chemical interaction was observed between CRI, lauryl ether, and aminoclay. However, the amorphization of CRI suggests the presence of weak molecular interactions, with lauryl ether facilitating solubilization through micelle formation and aminoclay potentially contributing via hydrogen bonding. | The cytotoxic effects of CRI and CRI-lauryl ether-aminoclay (CRI-TSD) were tested in HT29 cells. CRI-TSD showed a greater level of cytotoxicity ($CC_{50}$ value: 26.3 μM) than CRI ($CC_{50}$ value: 160 μM). | - | [98] |
| 19. | Docetaxel (DOCE) | β-cyclodextrin (β-CD) and HPMC E5 | Freeze-drying | FTIR research indicated the interaction of DOCE's main groups (-OH, -NH, C=O, C-O, C=C, and -CH) with β-CD in TSD due to the presence of HPMC E5. The HPMC E5 considerably improved the interaction of DOCE with β-CD. | Anticancer activity experiments using MCF-7 cell lines demonstrated enhanced cell growth suppression with DOCE-β-CD-HPMC E5 (DOCE-TSD). The $IC_{50}$ value of DOCE-TSD (22.08 μg/mL) was lower than that of DOCE-β-CD (DOCE-BSD) (27.52 μg/mL) and pure DOCE (36.93 μg/mL), indicating its superior anticancer activity. | - | [99] |
| 20. | Flufenamic acid (FLF) | β-cyclodextrin (β-CD) and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer | Solvent evaporation and microwave irradiation | Spectral analysis confirmed interactions between FLF, β-CD, and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer through hydrophobic forces (C=C stretching of FLF with the β-CD cavity, C–F shifts with polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), hydrogen bonding (O–H stretching of β-CD with FLF's hydroxyl groups, N–H stretching of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer with FLF), and van der Waals interactions ($CH_2$ bending and C–O–C stretching of the carriers with FLF). These interactions suggest the formation of a stable system without significant chemical bond formation. | - | FLF-β-CD-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (FLF-TSD) had a higher anti-inflammatory activity (67.63 ± 3.18%) than pure FLF (43.06 ± 3.27%) after 6 hours of oral treatment. | [100] |

**Abbreviations**: TSD, Ternary solid dispersion; BSD, Binary solid dispersion; FTIR, Fourier-Transform Infrared Spectroscopy; SIM, Simvastatin; PEG, Polyethylene Glycol; TC, Total cholesterol; TG, Triglycerides; HFD, High-fat diet; GLB, Glibenclamide; HME, Hot melt extrusion; CUR, Curcumin; HPMC, Hydroxypropyl methylcellulose; FIS, Fisetin; HPβ-CD, HP-beta-cyclodextrin; β-CD, Beta-Cyclodextrin; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; CUPRAC, Cupric Reducing Antioxidant Capacity; FRAP, Ferric Reducing Antioxidant Power; AChE, Acetylcholinesterase; BChE, Butyrylcholinesterase; LW6, 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid methyl ester; PVP, Povidone; BCRP, Breast cancer resistance protein; Cmax, Maximum concentration; Tmax, Time to reach Cmax; AUC, Area under curve; AST, Aspartate Aminotransferase; $CCl_4$, Carbon tetrachloride; SL or SM, Silymarin; KL, Kollidone VA64; PL, Poloxamer; MI, Microwave irradiation; FD, Freeze-drying; $IC_{50}$, Inhibition concentration 50%; ALT, Alanine Aminotransferase; TNF-α, Tumor necrosis factor-alpha; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; P-407, Poloxamer 407; KSR, Kollidon-SR; AD or AP, Andrographolide; OMT, Oxymatrine; pHCA, p-hydroxycinnamic acid; BR, Berberine; DIOS, Diosmin; AT or ATR, Atorvastatin; P188: Poloxamer 188; CCS, Ac-Di-Sol® SD-711; K, polyoxyl 40 hydrogenated castor oil; TAS, Total antioxidant status; Glc, Gliclazide; Tryp, Tryptophan; TOL, Toltrazuril; LOR, Lornoxicam; PRX, Piroxicam; GL, Gelucire 50/13; $CC_{50}$, Cytotoxic concentration 50%; CRI, Chrysin; DOCE, Docetaxel; FLF, Flufenamic acid.

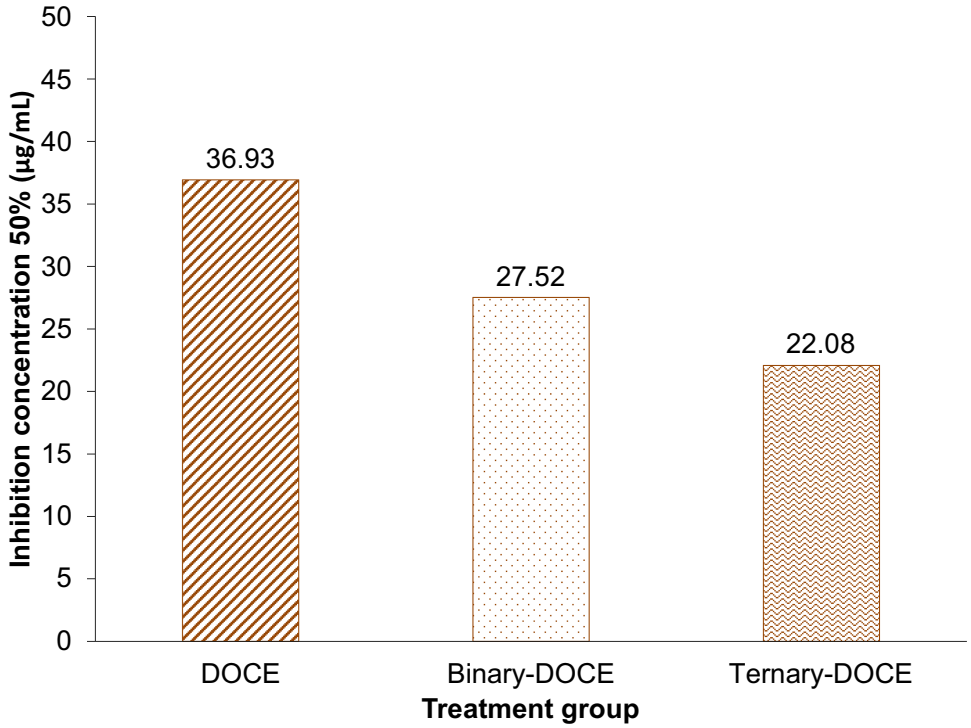


**Figure 4** The $IC_{50}$ values of pure DOCE, binary, and ternary DOCE formulations against MCF-7 breast cancer cells. Each bar represents the concentration (µg/mL) of formulation required to inhibit 50% of cell growth. DOCE: pure docetaxel. Binary-DOCE: docetaxel with β-cyclodextrin (β-CD). Ternary-DOCE: docetaxel with β-CD and hydroxypropyl methylcellulose (HPMC). Adapted from Mane PT, Wakure BS, Wakte PS. Ternary inclusion complex of docetaxel using β-cyclodextrin and hydrophilic polymer: Physicochemical characterization and in-vitro anticancer activity. *J Appl Pharm Sci.* 2022;12(12):150–161. Creative Commons.[99]

Recent studies on TSD highlight their potential to improve anticancer efficacy by enhancing drug solubility and bioavailability. Lee et al[98] assessed the cytotoxic effects of chrysin and TSD chrysin using lauryl ether and aminoclay in HT29 colorectal cancer cells. The TSD chrysin exhibited significantly greater cytotoxicity than pure chrysin, with a $CC_{50}$ of 26.3 µM, whereas pure chrysin exhibited no cytotoxicity even at 160 µM. The TSD formulation's enhanced solubility of chrysin was responsible for this improvement. Mane et al[99] similarly examined the anticancer properties of pure DOCE, binary, and ternary systems of DOCE on MCF-7 breast cancer cells. Figure 4 shows the ternary systems exhibited the highest cell growth inhibition ($IC_{50}$= 22.08 µg/mL), followed by the binary system (27,52 µg/mL), and pure DOCE (36.93 µg/mL). The increased inhibition resulted from heightened solubility and bioavailability via complexation with β-CD and HPMC, underscoring the critical role of solubility enhancement in augmenting anticancer efficacy.

## Anticholinesterase

Anticholinesterases inhibit cholinesterase enzymes, primarily acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which degrade acetylcholine.[102] By preventing this degradation, anticholinesterases augment acetylcholine levels, rendering them crucial for treating neurological disorders such as Alzheimer's disease.[103] However, the low solubility of many drug candidates limits their bioavailability, reducing therapeutic efficacy. Recent research has investigated novel formulations to address solubility constraints and improve anticholinesterase effectiveness, as evidenced by Rosiak et al.[85]

Rosiak et al[85] assessed the anticholinesterase activity of FIS, binary FIS-methacrylic acid-ethyl acrylate copolymer (FIS-BSD), and ternary FIS-methacrylic acid-ethyl acrylate copolymer-HP-β-cyclodextrin (FIS-TSD) employing a spectrophotometric technique, wherein enzyme inhibition was quantified by the color intensity of thiocholine generated on a 96-well plate. The inhibitory effects of FIS, FIS-BSD, and FIS-TSD on AChE and BChE were evaluated by comparing their absorbance with control samples (water). The results showed that pure FIS demonstrated minimal inhibitory efficacy (0.40% ± 0.03% for AChE and 3.64% ± 0.23% for BChE). However, improvements in solubility with BSD and TSD approaches significantly enhanced enzyme inhibition. The inhibition by FIS-BSD (AChE inhibition: ~20% and BChE inhibition: ~30%) was further

enhanced by FIS-TSD (39.91% ± 3.47% for AChE and 42.62% ± 1.01% for BChE), exceeding previous FIS formulations and illustrating the vital role of solubility improvement in augmenting neuroprotective efficacy.

## Anti-Inflammatory

Anti-inflammatory drugs reduce inflammation by obstructing the synthesis of pro-inflammatory mediators such as nitric oxide (NO), cytokines, and prostaglandins.[104] However, many APIs, especially in crystalline form, struggle to achieve anti-inflammatory efficacy due to inadequate solubility and bioavailability. Restricted solubility impedes absorption, diminishing their capacity to attain appropriate therapeutic concentrations at the target location.

Recent studies of TSD, including those by Sohn et al[19] and Ishtiaq et al,[84] have explored the potential to overcome solubility difficulties and enhance anti-inflammatory activity. Sohn et al[19] assessed the anti-inflammatory efficacy of piroxicam (PRX) and PRX-TSD using Poloxamer 407 (P407) and colloidal silica dioxide in LPS-induced RAW 264.7 cells. The research revealed that PRX samples diminished NO generation at a concentration of 25 μg/mL, with PRX-TSD exhibiting the most significant suppression (0.42 ± 0.01 μg/mL), followed by commercial piroxicam formulation (0.44 ± 0.01 μg/mL) and pure PRX (0.56 ± 0.01 μg/mL). PRX-TSD also exhibited the highest NO inhibition (26.6 ± 1.1%), signifying greater anti-inflammatory efficacy attributed to its enhanced solubility. Ishtiaq et al[84] similarly showed that TSD curcumin using HPMC E5 and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (CUR-TSD) markedly prevented protein denaturation (80% ± 3.16) in contrast to pure CUR (49% ± 2.91). The increased inhibition was ascribed to the superior solubility and bioavailability of CUR in the TSD, rendering it more efficacious against inflammatory processes.

## Antioxidant

Antioxidants counteract free radicals, preventing oxidative harm. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay is commonly used to evaluate this activity in vitro by measuring absorbance at 517 nm, where a decrease in the absorbance indicates stronger antioxidant activity.[105] Numerous crystalline active substances exhibit diminished antioxidant capacity owing to inadequate solubility, limiting their efficacy in free radical scavenging.

Several studies on TSD, including those by Anwer et al[92] and Ishtiaq et al[84] have demonstrated that enhancing solubility via TSD markedly improves antioxidant activity. Anwer et al[92] found that the TSD of DIOS using β-CD and PEG 6000 exhibited superior DPPH radical scavenging activity (75% at 100 μg/mL), outperforming DIOS-PEG 6000 (58–65%) and pure DIOS (25–55%). This improvement was attributed to the enhanced solubility within the TSD system, resulting in greater dissolution and radical scavenging efficacy. Similarly, Ishtiaq et al[84] reported that CUR-TSD demonstrated significantly higher antioxidant activity with a DPPH inhibition of 93% ± 5.30, compared to 69% ± 4.79 for pure CUR. The greater efficacy of CUR-TSD was attributed to its improved solubility, overcoming CUR's inherent poor solubility and augmenting its capacity to effectively scavenge free radicals.

## Antimicrobial

Antimicrobial activity refers to a compound's capacity to suppress or eradicate microorganisms, encompassing bacteria, fungi, viruses, and protists. Sun et al[96] investigated the inhibitory effects of TSD toltrazuril using $Ca(OH)_2$ and PEG 6000 (TOL-TSD) against *Toxoplasma gondii* and observed a marked increase in inhibition rates with elevated drug concentrations, particularly at lower doses. Nonetheless, the rate of growth inhibition diminished with increasing drug doses, reaching approximately 75% at 50 μg/mL and between 85% and 100% at 100 μg/mL. In comparison, TOL-BSD achieved inhibition rates of 60% and 70%, while pure TOL exhibited the lowest efficacy at 50% and 65%, respectively.

In addition to antiparasitic activity, enhancing solubility is vital for augmenting antibacterial efficacy. This was demonstrated by Ishtiaq et al[84] who evaluated the antibacterial activity of CUR and CUR-TSD against *Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa*, and *Escherichia coli*. The findings indicated that CUR-TSD demonstrated markedly superior antibacterial efficacy than pure CUR, as evidenced by larger zones of inhibition and reduced minimum inhibitory concentration (MIC) values. The reduced antibacterial activity of CUR was ascribed to its hydrophobic characteristics. In contrast, the superior efficacy of CUR-TSD was likely due to its enhanced solubility and improved bacterial cell membrane penetration, rendering it more potent against both Gram-positive and Gram-negative

bacteria. These results illustrate the importance of TSD in enhancing the bioavailability and antibacterial effectiveness of poorly soluble compounds.

## In vivo Studies of Ternary Solid Dispersion

### Anticancer

Bajracharya et al[86] assessed the co-administration of LW6, a BCRP inhibitor, with topotecan, a topoisomerase inhibitor, for metastatic ovarian carcinoma and small-cell lung cancer. Since BCRP limits topotecan's oral bioavailability, the study examined LW6's effect on enhancing its pharmacokinetics. The results showed a tenfold increase in topotecan's oral bioavailability with TSD-LW6 compared to pure LW6, highlighting the role of BCRP inhibition. The improved solubility and dissolution of TSD likely resulted in elevated LW6 concentrations in the intestinal lumen, thereby augmenting its inhibitory impact on BCRP. These findings highlight TSD's potential in optimizing oral bioavailability and therapeutic efficacy.

### Anti-Alzheimer

Andrographolide, a diterpene lactone, exhibits various pharmacological properties and has been explored as a potential treatment for Alzheimer's disease.[106] Serrano et al[107] demonstrated that andrographolide reduces β-amyloid (Aβ) levels and modulates amyloid plaque formation in the hippocampus and cortex of young mice, which improves cognitive deficits in both young and mature Aβ PPswe/PS-1 Alzheimer's disease mice models. Nonetheless, its poor water solubility and low oral bioavailability have hindered further clinical development.

Fang et al[90] examined the anti-Alzheimer's efficacy of ternary co-amorphous andrographolide (AP-TSD) using OMT and pHCA in *Caenorhabditis elegans* as an in vivo model. The AP-TSD formulations were safe (Figure 5), exhibiting no significant decline in survival rates, even at high concentrations. Compared to crystalline AP, AP-TSD significantly delayed nematode paralysis caused by Aβ aggregation, with the AP-TSD system exhibiting the strongest anti-Alzheimer's effects. The findings indicate that TSD-based formulation could enhance stability, solubility, and pharmacological activity, presenting a promising strategy for the treatment of Alzheimer's disease.

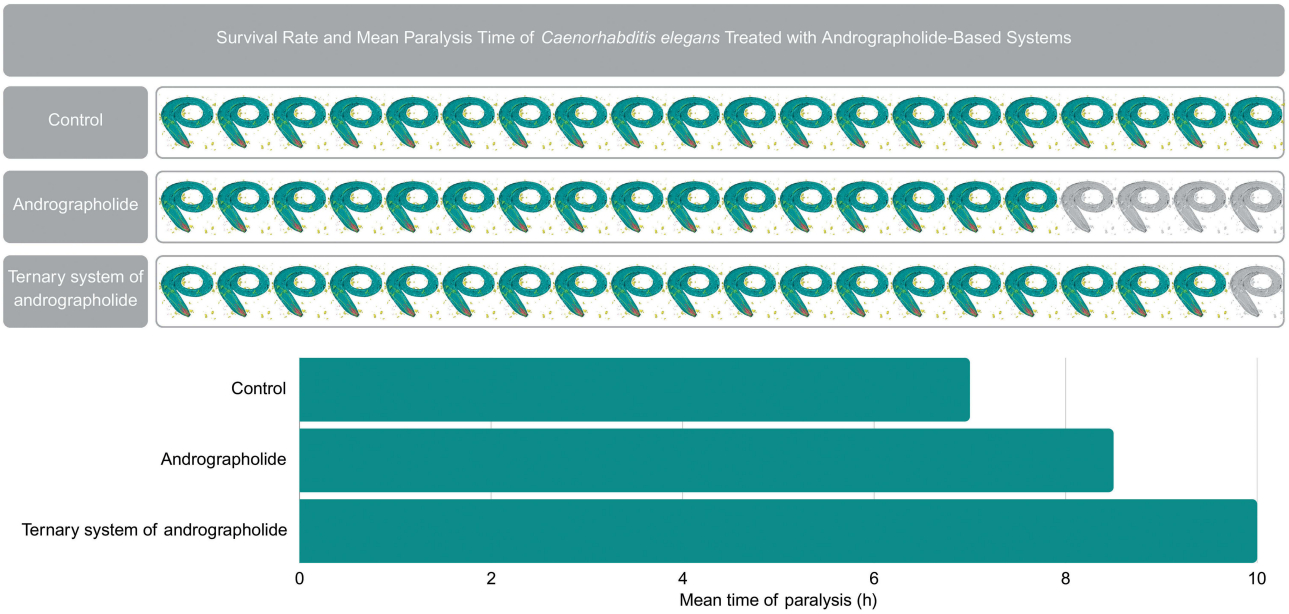


**Figure 5** Visualization of *Caenorhabditis elegans* survival rate and mean paralysis time under different treatments. Pictogram rows (top): Each worm icon represents 5% of the total *C. elegans* population. Teal worms = alive/active (not paralyzed), gray worms = dead/paralyzed. Bar chart (bottom): Shows the mean time to paralysis (hours) for each treatment group. Control refers to *C. elegans* without active compound, while andrographolide represents the pure active compound. The ternary system of andrographolide consists of andrographolide formulated with oxymatrine (OMT) and p-hydroxycinnamic acid (pHCA). Adapted from *Eur J Pharm Biopharm*. Volume 181. Fang X, Hu Y, Yang G, Shi W, Lu S, Cao Y. Improving physicochemical properties and pharmacological activities of ternary co-amorphous systems. 22–35, Copyright 2022, with permission from Elsevier.[90]

## Anti-Hyperlipidemic

Faraji et al[93] and Torrado-Salmerón et al[94] reported enhanced antihyperlipidemic efficacy of TSD atorvastatin (AT-TSD) in high-fat diet (HFD)-induced hyperlipidemia rats compared to pure AT. Faraji et al[93] found that pure AT reduces triglyceride (TG) and total cholesterol (TC) levels after 14 days ($p < 0.01$), while TSD and PM formulations showed greater lipid-lowering effects ($p < 0.001$) due to improved solubility and absorption. Torrado-Salmerón et al[94] demonstrated that AT-TSD using CCS and K significantly reduced TC, TG, and low-density lipoprotein (LDL) levels while preserving high-density lipoprotein (HDL) concentrations. This effect was attributed to increased AT permeability and P-glycoprotein inhibition by surfactants, facilitating hepatic lipid clearance and lipogenesis suppression. These findings highlight AT-TSD's ability to improve antihyperlipidemic therapy by addressing solubility limitations.

The TSD system has also shown the antihyperlipidemic efficacy of simvastatin (SIM). Mahboobian et al[82] demonstrated the antihyperlipidemic efficacy of SIM-TSD using polyoxyl 40 stearate and PEG 12000. On day 14, SIM-TSD significantly reduced TC levels ($p < 0.001$) and limited the TG increase to 4.70%, as compared to 65.52% in the HFD group. Unlike PM and pure SIM, which showed no significant effects, SIM-TSD exhibited an improved solubility and dissolution, resulting in greater in vivo efficacy. The study confirmed the significance of hydrophilic carriers and surfactants in enhancing drug wettability and absorption, in line with the findings on AT and rosuvastatin described earlier.

## Anti-Inflammatory

The TSD system enhances the anti-inflammatory efficacy of poorly soluble drugs. Amin and Hussain[97] revealed that TSD lornoxicam using polyethylene glycol glycerides and polysorbate 80 (LOR-TSD) reduced paw edema by 50% relative to the binary system (60%) and the pure drug (70%). Alshehri et al[100] showed that FLF-TSD using β-CD and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer achieved 67.63% inhibition, compared to 43.06% for pure FLF after six hours. Haq et al[89] confirmed that AD-TSD using KSR and Poloxamer 407 improved inflammation control compared to pure AD in mitigating carrageenan-induced paw edema and ameliorating arthritic conditions in Wistar rats. These findings underscore the potential of TSD in improving drug solubility, absorption, and therapeutic efficacy for anti-inflammatory agents.

## Anti-Hypoglycemic

Pisay et al[83] established that TSD glibenclamide using polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and Poloxamer 407 (GLB-TSD) markedly improved anti-hypoglycemic efficacy in comparison to pure GLB and the commercially available product. In type II diabetic Sprague-Dawley rats, GLB-TSD rapidly lowered blood glucose ($128 \pm 17$ mg/dL at 0.5 hours) and sustained lower glucose levels for 4 hours. This was ascribed to an almost three-fold augmentation in oral bioavailability, which was proven to be statistically significant in comparison to the non-TSD form of the drug ($p < 0.005$).

## Anti-Diabetic

The antidiabetic efficacy can be improved by the TSD system, as evidenced by the research conducted by Zhaojie et al[91] Their research showed that TSD of berberine using sodium caprate and PEG 6000 (BR-TSD) showed a significantly improved efficacy. At 25 mg/kg, BR-TSD reduces fasting blood glucose, TC, and TG levels in diabetic rats, comparable to berberine (100 mg/kg) and commercial tablets. At 100 mg/kg, BR-TSD surpassed berberine and metformin in hypoglycemic and triglyceride-lowering effects, highlighting its potential for type II diabetes treatment.

## Hepatoprotective

Hwang et al[87] examined the hepatoprotective properties of SL-TSD via in vivo research utilizing $CCl_4$-induced hepatotoxicity in rats. The findings indicated that SL-TSD significantly reduces aspartate transaminase (AST) levels and liver deterioration, unlike SL powder and commercial formulations. Similarly, Torrado-Salmerón et al[94] reported that AT-TSD using CCS and K alleviated high-fat diet-induced liver injury, reducing steatosis, inflammation, and hepatocyte ballooning compared to the pure AT group. This API also resulted in a substantial drop in the non-alcoholic fatty liver disease (NAFLD) activity score (NAS), indicating a reduction in liver damage and an enhancement in liver function.

## Discussion and Author's Perspective

TSDs offer an advanced formulation strategy to enhance the solubility and bioavailability of poorly soluble APIs. Unlike BSDs, which involve dispersing an API within a polymer matrix, TSDs integrate a third component to improve the physicochemical characteristics of the formulation. The primary objective of TSD development is to enhance drug dissolution and stability, addressing the issues associated with the restricted solubility of numerous novel therapeutic candidates. By overcoming these challenges, TSDs offer a promising strategy for enhancing drug absorption and optimizing therapeutic effects, ultimately leading to enhanced pharmacological activity and stronger interactions with biological systems.

To comprehensively evaluate the therapeutic potential of TSDs, in vitro and in vivo studies are crucial to assess their impact on the pharmacological activity of the formulated APIs. In vitro studies provide a controlled laboratory environment to examine the formulation's interactions with biological systems at the cellular level, offering preliminary insights into efficacy and potential therapeutic advantages. Conversely, in vivo studies seek to assess TSD formulations in living creatures to ascertain the therapeutic efficacy of the drug in systemic circulation and its dynamic consequences.

The pharmacological advantages of TSDs can be predicted using theoretical models, such as the Conductor-like Screening Model for Real Solvents (COSMO-RS) and machine learning models.[108,109] While these models indirectly assess pharmacological activity, they estimate key formulation parameters—such as solubility, miscibility, and physical stability—that are strongly associated with therapeutic outcomes. These theoretical models are further supported by in vitro and in vivo studies. In vitro studies have indicated that TSDs can increase cellular uptake and improve pharmacological responses across various disease models. Research has indicated that TSDs could significantly enhance antioxidant, anti-inflammatory, anticancer, antibacterial, and anticholinesterase activities, highlighting their potential for optimizing drug performance.

Through in vivo studies, TSD formulations have demonstrated significant improvement in the bioavailability of poorly soluble drugs by increasing plasma concentrations, accelerating absorption, and enhancing the therapeutic efficacy of various pharmacological agents, including antihyperlipidemic, anticancer, anti-inflammatory, anti-hypoglycemic, anti-Alzheimer's, antidiabetic, antioxidant, antibacterial, and hepatoprotective drugs. These findings demonstrate the ability of TSDs to optimize drug delivery by improving the pharmacokinetic and pharmacodynamic properties of APIs.

The enhancement of pharmacological efficacy by a TSD system is attributed to an increased solubility, stability, and bioavailability of the active compounds, as illustrated in Figure 6. Many crystalline APIs exhibit strong intermolecular interactions and high lattice energy, leading to thermodynamic stability but poor aqueous solubility. Overcoming this lattice energy is crucial for dissolution, often resulting in slow dissolution rates and restricted bioavailability. BSD systems address this limitation by adding hydrophilic carriers to diminish lattice energy and improve solubility. By interacting with the polymer, the crystalline structure is partially disrupted, transforming the drug into an amorphous state with lower lattice energy and greater molecular mobility. Nonetheless, some BSDs still suffer from limited wettability and dissolution rates, which restrict API absorption. TSDs introduce a third component to further optimize these properties, improving solubility, dissolution, and bioavailability.

TSD systems offer an advanced approach to improving drug solubility, stability, and absorption through the addition of an extra component, such as a polymer, surfactant, or other excipients. By significantly reducing lattice energy, TSDs promote the transformation of drugs into a high-energy amorphous state with enhanced molecule mobility and diminished intermolecular interactions, leading to improved solubility and bioavailability. These systems enhance drug wettability, reduce particle size, and inhibit recrystallization, ensuring prolonged supersaturation. Additionally, TSDs facilitate molecular-level API dispersion, accelerate dissolution, improve membrane permeability, and inhibit efflux transporters that limit drug absorption. The synergistic effects of drug carriers in TSD formulations optimize interactions with biological membranes, enabling more effective drug delivery and subsequently demonstrating superior efficacy across various pharmaceutical applications.

Despite the promising advantages of TSD systems, several formulation and scale-up challenges remain. From a formulation perspective, the selection of appropriate ratios and combinations of the API, polymer, and third component is critical, as their physicochemical interactions substantially influence solubility enhancement, physical stability, and pharmacokinetic efficacy. Maintaining the amorphous state of the API, essential for enhanced solubility, requires stringent control over

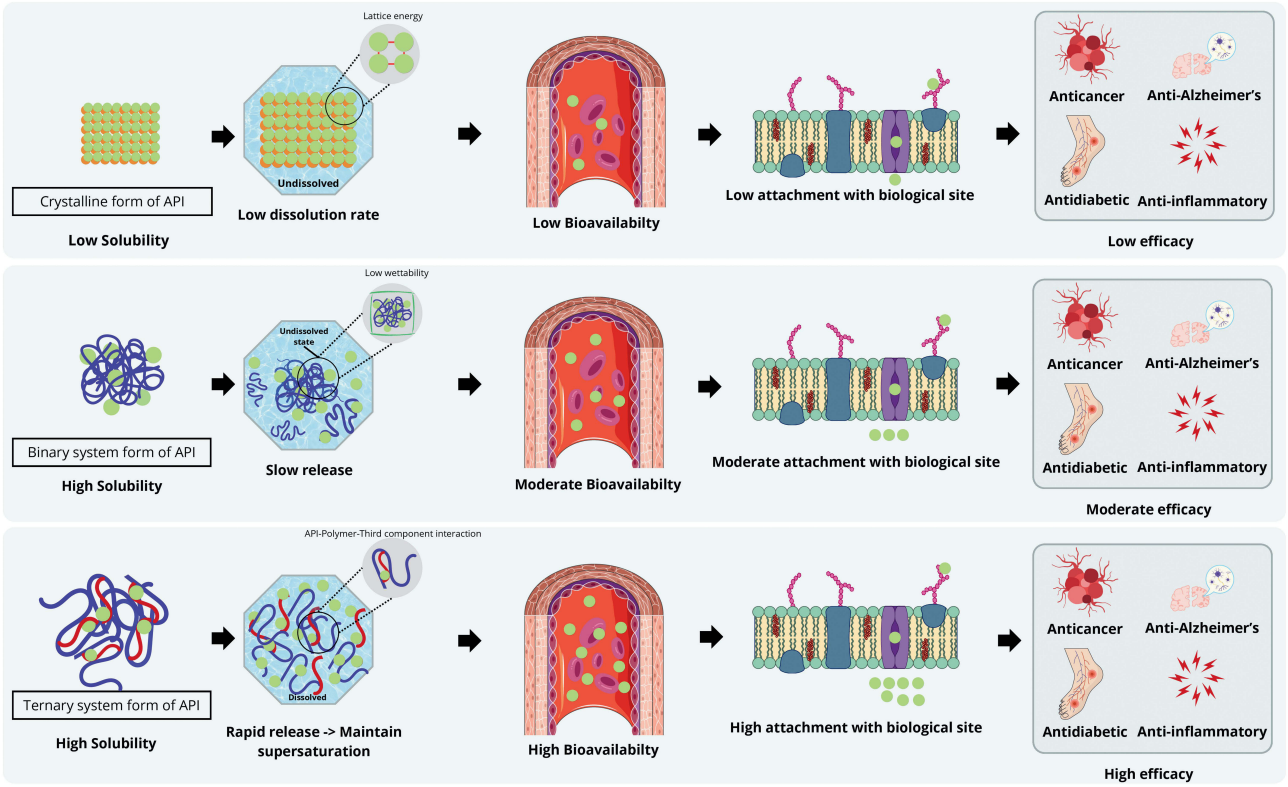


**Figure 6** The proposed mechanism underlying the enhancement of the pharmacological activity of active pharmaceutical ingredients in ternary solid dispersion systems.
**Abbreviation**: API, active pharmaceutical ingredients.

processing parameters such as temperature, solvent evaporation rate, and mixing homogeneity. Suboptimal formulation or processing may lead to recrystallization, phase separation, or chemical degradation, ultimately reducing therapeutic performance. Moreover, the addition of a third component introduces additional complexity, necessitating comprehensive compatibility assessments with both the API and polymer to ensure stability and prevent adverse interactions.

Furthermore, the rational design of TSD formulations requires critical evaluation of third components, such as polymers, surfactants, acids/bases, pH modulators, adsorbents, and small molecule additives, due to their pivotal role in modulating intermolecular interactions, stabilizing the amorphous phase, and enhancing dissolution. Their compatibility with both the API and primary polymer matrix is essential to prevent recrystallization, phase separation, or chemical degradation. However, these components may pose risks related to toxicity, metabolic effects, or regulatory compliance. For example, certain surfactants can exhibit dose-dependent cytotoxicity or unintended membrane interactions, while emerging additives often lack comprehensive safety data. Although polymers such as PVP and HPMC are generally recognized as safe and effective crystallization inhibitors, their performance can vary depending on the API's properties. Similarly, adsorbents and pH modifiers can improve stability and microenvironmental solubility but require careful characterization to avoid unintended interactions. Novel lipids and polymeric carriers offer promising functionality but demand thorough preclinical evaluation due to limited toxicological data. Thus, selection of third components must be determined by their functional efficacy in vitro, as well as their biocompatibility, toxicological profile, regulatory status, and suitability for long-term therapeutic use.

From a manufacturing perspective, scaling up TSD formulations using techniques such as hot-melt extrusion, spray drying, or solvent evaporation introduces significant technical challenges. Achieving consistent product quality and batch-to-batch reproducibility requires precise control over critical process parameters, including feeding rate, mixing duration, drying efficiency, residual solvent content, and particle size distribution. Equipment limitations and operational complexity often lead to increased production costs and extended processing times. Additionally, maintaining the long-term physical and chemical stability of the amorphous form during storage and distribution remains a major concern.


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These scale-up and stability issues necessitate systematic process development using design-of-experiment (DoE) studies, real-time process monitoring, and rigorous long-term stability testing under various environmental conditions.

Cost-effectiveness is a crucial consideration for the industrial viability of TSD formulations. The reliance on specialized carriers, high-performance excipients, and advanced manufacturing technologies can substantially elevate production costs. Therefore, developing economically feasible TSDs requires strategic excipient selection, simplification of production processes, and, where possible, the addition of cost-efficient third components that deliver comparable functional benefits without compromising product performance.

Regulatory approval of TSD products necessitates comprehensive physicochemical characterization, toxicological assessment, long-term stability studies, and validated manufacturing protocols. These requirements highlight the importance of systematic preclinical and pharmacokinetic investigations, supported by rigorous quality assurance protocols, to ensure successful clinical translation and eventual commercialization of TSD-based drug products.

Future research should focus on optimizing TSD formulations to enhance reproducibility and therapeutic efficacy for clinical applications. Key areas of exploration include refining amorphization techniques, selecting the optimal third component, and improving processing methodologies to enhance drug release and bioavailability. The exploration and addition of novel surfactants, polymers, and excipients hold significant promise for expanding the applicability of TSDs across a broader range of APIs, particularly those with challenging physicochemical properties.

Emerging research directions involve the integration of high-throughput formulation screening and machine learning-based predictive modeling to efficiently identify optimal TSD combinations. Comprehensive pharmacokinetic, toxicological, and preclinical studies remain critical to elucidate the in vivo behavior, safety profile, and systemic effects of TSDs, especially when adding novel or less-characterized excipients. The development of robust in vitro–in vivo correlation (IVIVC) models, alongside long-term physical stability assessment and detailed toxicity studies, both acute and subchronic, will be essential to support regulatory submissions and clinical translation. Collectively, these focused research strategies will significantly enhance the translational potential of TSD systems and accelerate their adoption into advanced pharmaceutical development pipelines.

## Conclusion

In conclusion, TSDs significantly enhance the solubility, stability, and pharmacological efficacy of poorly soluble drugs. The addition of a third component in TSD formulations improves drug solubility, prolongs supersaturation, and prevents recrystallization, resulting in superior bioavailability and therapeutic outcomes. In vitro and in vivo studies consistently demonstrate that TSD-based formulations outperform BSDs in dissolution, absorption, and pharmacological optimization across various therapeutic applications. These advancements reinforce the potential of TSDs in drug development, particularly for oral drug administration. However, challenges in large-scale production, cost-effectiveness, and regulatory compliance must be addressed for successful clinical and commercial transition. Overcoming these barriers will maximize TSDs' therapeutic benefits and broaden their role in modern pharmacology.

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## Disclosure

The authors declare that there are no conflicts of interest related to the content of this article.

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